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# 36736 Access DB# \_\_\_\_\_ SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Dwayne C. Ince Examiner #: \_\_\_\_\_ Date: 27 FEB 01  
 Art Unit: R14 Phone Number 301-4674 Serial Number: 09158-403  
 Mail Box and Bldg/Room Location: \_\_\_\_\_ Results Format Preferred (circle): PAPER DISK E-MAIL  
2001/207

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 Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: see attached

Inventors (please provide full names): \_\_\_\_\_

Earliest Priority Filing Date: 27 APR 1999

*\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

*Please read generic claim 1  
 claim 10 and  
 the compound of claim 15*

*claim 3- Please give examples of age-related behavioral disorders.*

**POINT OF CONTACT:**  
**BARB O'BRYEN**  
**TECH. INFORMATION SPECIALIST**  
**STIC CM1 12C14 308-4291**

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expts.) using microdialysis and behavioral techniques. Twenty-four rats after the last treatment, cortical ACh levels were significantly higher in rats subchronically treated with HEP than in rats treated with saline. AChE activity was still inhibited in cortex, hippocampus and striatum. The injection of a challenge dose of HEP (0.6 mg/kg s.c.) 24 h after the last treatment produced a faster and a more sustained increase of ACh in the cortex of subchronically treated rats compared to those repeatedly injected with saline. However, the max. increase of ACh levels after injection of the challenge was comparable in both groups. In an object recognition test in which the pretest and test phase were spaced by 45 days, HEP prevented the deterioration of spatial memory occurring during this period, but had no effect on non-spatial memory. The present results suggest that moderate inhibition of brain AChE is able to maintain high levels of cortical extracellular ACh in aged rats and that this increase matches facilitatory effect of HEP on spatial memory.

IT 9000-81-1, **Acetylcholinesterase**

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(effect of subchronic treatment with the **acetylcholinesterase inhibitor** heptastigmine on central cholinergic transmission and memory impairment in aged rats)

L164 ANSWER 46 OF 71 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:533469 CAPLUS

DOCUMENT NUMBER: 129:254877

TITLE: Effect of subchronic treatment with metrifonate and tacrine on brain cholinergic function in aged F344 rats

AUTHOR(S): Giovannini, Maria Grazia; Scali, Carla; Bartolini, Luciano; Schmidt, Bernard; Pepeu, Giancarlo  
CORPORATE SOURCE: Department of Preclinical and Clinical Pharmacology, University of Florence, Florence, 50134, Italy

SOURCE: ~~Eur. J. Pharmacol.~~ (1998), 354(1), 17-24  
CODEN: EJPHAZ; ISSN: 0014-2999

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of 21-day treatment with the acetylcholinesterase inhibitors metrifonate (80 mg kg<sup>-1</sup> per os (p.o.)) and tacrine (3 mg kg<sup>-1</sup> p.o.), twice daily, on cortical and hippocampal cholinergic systems were investigated in aged rats (24-26 mo). Extracellular acetylcholine levels were measured by transversal microdialysis in vivo; choline acetyltransferase and acetylcholinesterase activities were measured ex vivo by radiometric methods. Basal cortical and hippocampal extracellular acetylcholine levels, measured 18 h after the last metrifonate treatment, were about 15 and two folds higher, resp., than in control and tacrine-treated rats. A challenge with metrifonate further increased cortical and hippocampal acetylcholine levels by about three and four times, resp. Basal extracellular acetylcholine levels, measured 18 h after the last treatment with tacrine were not statistically different from those of the control rats. A challenge with tacrine increased cortical and hippocampal extracellular acetylcholine levels by about four and two times. A 75% inhibition of cholinesterase activity was found 18 h after the last metrifonate administration, while only a 15% inhibition was detectable 18 h after the last tacrine administration. The challenge with metrifonate or tacrine resulted in 90 and 80% cholinesterase inhibition, resp. These results demonstrate that in aging rats a subchronic treatment with metrifonate results in a long-lasting, cholinesterase inhibition, and a persistent increase in acetylcholine extracellular levels which compensate for the age-assocd. cholinergic hypofunction. Metrifonate is therefore a potentially useful agent for the cholinergic deficit accompanying Alzheimer's disease.

IT 9000-81-1, **Acetylcholinesterase**

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CORPORATE SOURCE:  
SOURCE:

CAPLUS COPYRIGHT 2001 ACS

1997:735087 CAPLUS

128:43758

Metrifonate improves associative learning and retention in aging rabbits

Kronforst-Collins, M. A.; Moriearty, P. L.; Schmidt, B.; Disterhoft, J. F.

Department of Cell and Molecular Biology, Institute for Neuroscience, Northwestern University Medical School, Chicago, IL 60611-3008, USA

Behav. Neurosci. 111(5), 1031-1040

CODEN: BENEDJ; ISSN: 0735-7044

American Psychological Association

Journal

English

SOURCE:

PUBLISHER:

DOCUMENT TYPE:

LANGUAGE:

AB The cholinergic system is known to show deterioration during aging and Alzheimer's disease (AD). In response, a therapeutic approach to AD has been to attempt to compensate for the decrease in central cholinergic function by potentiating the activity of the remaining intact cholinergic cells with cholinesterase (ChE) inhibitors. In this study treatment with the long-lasting ChE inhibitor metrifonate facilitated acquisition and retention of eyeblink conditioning in aging rabbits. Metrifonate treatment resulted in steady-state, dose-dependent acetylcholinesterase (AChE) inhibition in red blood cells. Maximal behavioral efficacy was achieved with AChE inhibition of approx. 40%, with no further improvements resulting from increased levels of inhibition. Metrifonate was behaviorally effective in the absence of the severe side effects that can plague ChE inhibitors, supporting metrifonate as a possible treatment for the cognitive deficits resulting from normal aging and AD.

IT 9000-81-1, Acetylcholinesterase

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(metrifonate improves associative learning and retention in aging rabbits in relation to acetylcholinesterase inhibition and treatment of Alzheimer's disease)

L164 ANSWER 51 OF 71 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:242145 CAPLUS

DOCUMENT NUMBER: 126:271701

TITLE: Donepezil

AUTHOR(S): Bryson, Harriet M.; Benfield, Paul

CORPORATE SOURCE: Adis International Limited, Auckland, N. Z.

SOURCE: Drugs Aging (1997), 10(3), 234-239

CODEN: DRAGE6; ISSN: 1170-229X

PUBLISHER: Adis

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 26 refs. Donepezil is a specific and potent acetylcholinesterase inhibitor according to in vitro data. It displays primarily noncompetitive inhibitory activity. In vivo, donepezil inhibited acetylcholinesterase activity in human erythrocytes and increased extra-cellular acetylcholine levels in the cerebral cortex and hippocampus of the rat. Donepezil demonstrated efficacy in tests of ref. memory in animals, but had less consistent activity in tests of working memory. Donepezil 5 or 10 mg/day was assocd. with significant improvements in cognitive function [assessed by the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog)] after 14 and 30 wk and patient global function (Clinician's Interview-based Impression of Change incorporating caregiver input score) after 30 wk, compared with placebo, in patients with mild to moderate Alzheimer's disease. After 2 yr, donepezil 5 or 10 mg/day was assocd. with an ADAS-cog score approx. 4 points better than would be expected in untreated patients with mild to

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moderate Alzheimer's disease. The most common adverse events reported in association with donepezil 5 mg/day were gastrointestinal events (nausea/vomiting, diarrhea, gastric upset and constipation) and dizziness. No hepatotoxicity was reported after 12 wk' treatment.

IT 9000-81-1, **Acetylcholinesterase**

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor; donepezil pharmacodynamics and pharmacokinetics)

L164 ANSWER 52 OF 71 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:123307 CAPLUS

DOCUMENT NUMBER: 126:220296

TITLE: Synthesis and preliminary structure-activity relationships of 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-1H-indol-5-yl methyl carbamate (P10358), a novel **acetylcholinesterase inhibitor**

AUTHOR(S): Martin, Lawrence L.; Davis, Larry; Klein, Joseph T.; Nemoto, Peter; Olsen, Gordon E.; Bores, Gina M.; Camacho, Fernando; Petko, Wayne W.; Rush, Douglas K.; et al.

CORPORATE SOURCE: Hoechst Marion Roussel Inc., Neuroscience Therapeutic Area, Bridgewater, NJ, 08807-0800, USA

SOURCE: Biorg. Med. Chem. Lett. (1997), 7(2), 157-162  
CODEN: BMCLE8; ISSN: 0960-894X

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of carbamate analogs of besipirdine (HP 749) was synthesized as potential agents with enhanced cholinomimetic properties for the treatment of Alzheimer's disease. P10358, 1-[(3-fluoro-4-pyridinyl)amino]-3-methyl-1H-indol-5-yl Me carbamate, emerged as a potent, reversible acetylcholinesterase inhibitor that significantly enhanced performance on oral or parenteral administration in learning and memory paradigms.

IT 9000-81-1, **Acetylcholinesterase**

RL: BSU (Biological study, unclassified); BIOL (Biological study) (synthesis and structure-activity relationships of besipirdine carbamate analogs as **acetylcholinesterase inhibitors**)

L164 ANSWER 53 OF 71 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:32874 CAPLUS

DOCUMENT NUMBER: 126:70552

TITLE: Effect of TAK-147, a novel AChE inhibitor, on cerebral energy metabolism

AUTHOR(S): Nakayama, Takahiro; Takahashi, Hideki; Miyamoto, Masaomi; Goto, Giichi; Nagai, Yasuo

CORPORATE SOURCE: Pharmaceutical Research Laboratories I, Takeda Chemical Industries, Ltd., Osaka, 532, Japan

SOURCE: Neurobiol. Aging (1996), 17(6), 849-857  
CODEN: NEAGDO; ISSN: 0197-4580

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Effect of TAK-147, a novel acetylcholinesterase (AChE) inhibitor, on cerebral energy metab. was investigated using an in vivo 31P-magnetic resonance spectroscopy (31P-MRS) technique and the autoradiog. 2-deoxy-[14C]-D-glucose method in aged Fischer 344 rats. We revealed that high-energy phosphate metabolites, phosphocreatine (PCr) and ATP, in the brain decreased gradually with aging and that significant decrement of cerebral PCr and ATP was obsd. from 13- and 8.5-mo-old in comparison with those of 2.5-mo-old rats, resp. Daily oral administration of TAK-147 (1 mg/kg) for 40 days increased PCr and ATP levels in aged rats (29-mo-old). To det. the site at which TAK-147 acts to increase high-energy phosphate

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metab., we investigated the rate of local cerebral glucose utilization (LCGU) in various brain regions. The rate of LCGU decreased in almost all brain regions in aged rats (28 mo of age), and the decrease was significant in 29 out of the 35 regions. When TAK-147 was administered orally to the aged rats, the levels were dose dependently increased, esp. in the auditory cortex. These results indicate that TAK-147 increases cerebral energy metab. in aged rats.

IT 9000-81-1, **Acetylcholinesterase**

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibitor; effect of **acetylcholinesterase**  
inhibitor TAK-147 on cerebral energy metab. in aged rats)

L164 ANSWER 54 OF 71 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:193684 CAPLUS

DOCUMENT NUMBER: 126:207463

TITLE: **Huperzine A, a novel promising  
acetylcholinesterase inhibitor**

AUTHOR(S): Cheng, Dong Hang; Ren, Hua; Tang, Xi Can

CORPORATE SOURCE: State Key Laboratory of Drug Research, Shanghai  
Institute of Materia Medica, Chinese Academy of  
Sciences, Shanghai, 200031, Peop. Rep. China

SOURCE: **NeuroReport** (1996), 8(1), 97-101

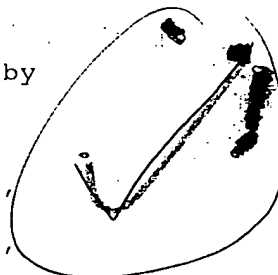
CODEN: NERPEZ; ISSN: 0959-4965

PUBLISHER: Rapid Science Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **The effects of huperzine A (I) on memory impairments (amnesia) induced by scopolamine (a model for human dementia) were evaluated using a radial maze task and inhibition of cholinesterase in vitro compared with the effects of E 2020 (II) and tacrine (III). Scopolamine (0.2 mg/kg) significantly impaired spatial memory in rats. I (0.1-0.4 mg/kg, p.o.), II (0.5-1.0 mg/kg, p.o.) and IIIe (1.0-2.0 mg/kg, p.o) were able to reverse these scopolamine-induced memory deficits. The ratios of I, II, and III for butyrylcholinesterase:acetylcholinesterase detd. by a colorimetric method were 884.57, 489.05, and 0.80, resp. The results demonstrated that I was the most selective acetylcholinesterase inhibitor, and improved the working memory deficit induced by scopolamine significantly better than did II or III, suggesting it may be a promising agent for clin. therapy of cognitive impairment in patients with Alzheimer's disease.**



IT 9000-81-1, **Acetylcholinesterase**

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
(huperzine A, a novel promising **acetylcholinesterase**  
inhibitor for clin. therapy of cognitive impairment in patients  
with Alzheimer's disease)

L164 ANSWER 55 OF 71 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 2000037532 EMBASE

TITLE: Regulating and assessing risks of cholinesterase-inhibiting pesticides: Divergent approaches and interpretations.

AUTHOR: Carlock L.L.; Chen W.L.; Gordon E.B.; Killeen J.C.; Manley A.; Meyer L.S.; Mullin L.S.; Pendino K.J.; Percy A.; Sargent D.E.; Seaman L.R.; Svanborg N.K.; Stanton R.H.; Tellone C.I.; Van Goethem D.L.

CORPORATE SOURCE: L.L. Carlock, Toxicology and Regulatory Consulting, 6343  
38th Ave. S.W., Seattle, WA 98126, United States

SOURCE: Journal of Toxicology and Environmental Health - Part B,  
(1999) 2/2 (105-160).

Refs: 69

ISSN: 1093-7404 CODEN: JTECFR

COUNTRY: United States

DOCUMENT TYPE: Journal; General Review

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agents, both of which increase cortical cholinergic activity.

L164 ANSWER 25 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS  
 ACCESSION NUMBER: 1997:457426 BIOSIS  
 DOCUMENT NUMBER: PREV199799756629  
 TITLE: Pontine nitric oxide modulates acetylcholine release, rapid eye movement sleep generation, and respiratory rate.  
 AUTHOR(S): Leonard, Timothy O.; Lydic, Ralph (1)  
 CORPORATE SOURCE: (1) Dep. Anesthesia, Pennsylvania State Univ., Coll. Med., Hershey, PA 17033, USA  
 SOURCE: [REDACTED]

ISSN: 0270-6474.  
 DOCUMENT TYPE: Article  
 LANGUAGE: English  
 AB

Pontine cholinergic neurotransmission is known to play a key role in the regulation of rapid eye movement (REM) sleep and to contribute to state-dependent respiratory depression. Nitric oxide (NO) has been shown to alter the release of acetylcholine (ACh) in a number of brain regions, and previous studies indicate that NO may participate in the modulation of sleep/wake states. The present investigation tested the hypothesis that inhibition of NO synthase (NOS) within the medial pontine reticular formation (mPRF) of the unanesthetized cat would decrease ACh release, inhibit REM sleep, and prevent cholinergically mediated respiratory depression. Local NOS inhibition by microdialysis delivery of NG-nitro-L-arginine (NLA) significantly reduced ACh release in the cholinergic cell body region of the pedunculopontine tegmental nucleus and in the cholinoceptive mPRF. A second series of experiments demonstrated that mPRF microinjection of NLA significantly reduced the amount of REM sleep and the REM sleep-like state caused by mPRF injection of the cholinergic inhibitor, physostigmine. Duration but not frequency of REM sleep epochs was significantly decreased by mPRF NLA administration. Injection of NLA into the mPRF before neostigmine injection also blocked the ability of neostigmine to decrease respiratory rate during the REM sleep-like state. Taken together, these findings suggest that mPRF NO contributes to the modulation of ACh release, REM sleep, and breathing.

L164 ANSWER 26 OF 71 BIOSIS COPYRIGHT 2001 BIOSIS  
 ACCESSION NUMBER: 1997:505567 BIOSIS  
 DOCUMENT NUMBER: PREV199799804770  
 TITLE: Tacrine response: Review of two years of prescription.  
 AUTHOR(S): Augry, F.; Darchy, A.; De Rotrou, J.; Guelfi, M. C. (1); Forette, F.  
 CORPORATE SOURCE: (1) Serv. Pharmacie, Hopital Broca, 54-56 rue Pascal, 75013 Paris France  
 SOURCE: Journal de Pharmacie Clinique, 1997, Vol. 16, No. 3, pp. 183-187.  
 ISSN: 0291-1981.

DOCUMENT TYPE: Article  
 LANGUAGE: French  
 SUMMARY LANGUAGE: French, English  
 AB

Alzheimer's disease is a degenerative disease leading to dementia associated with anatomic-pathologic and neurochemical modifications which induce a deterioration of the cholinergic system. The main clinical signs are: cognitive distress, intellectual confusion and performance difficulties. Psychometric tests as MMSE (mini mental state examination) and Adas-Cog (cognitive function of Alzheimer's disease assessment scale) can evaluate the cognitive functions. Tacrine response: The treatments were: 40 mg daily of tacrine for 6 weeks, 80 mg/d next 6 weeks, 120 mg/d for 2 months and finally 160 mg/d. The aim of our work was to analyse the

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